



US009168138B2

(12) **United States Patent**
O'Neil et al.

(10) **Patent No.:** **US 9,168,138 B2**
(45) **Date of Patent:** **Oct. 27, 2015**

(54) **ASPIRATING IMPLANTS AND METHOD OF BONY REGENERATION**

2310/00023 (2013.01); A61F 2310/00029 (2013.01); A61F 2310/00203 (2013.01); A61F 2310/00239 (2013.01)

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(58) **Field of Classification Search**
CPC A61F 2/441; A61F 2/4465; A61F 2/4611
USPC 623/17.11–17.16
See application file for complete search history.

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Assistant Examiner — Nicholas Plionis

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 824 days.

(21) Appl. No.: **12/634,647**

(22) Filed: **Dec. 9, 2009**

(65) **Prior Publication Data**

US 2011/0137418 A1 Jun. 9, 2011

(51) **Int. Cl.**

A61F 2/44 (2006.01)

A61F 2/28 (2006.01)

A61F 2/46 (2006.01)

A61F 2/30 (2006.01)

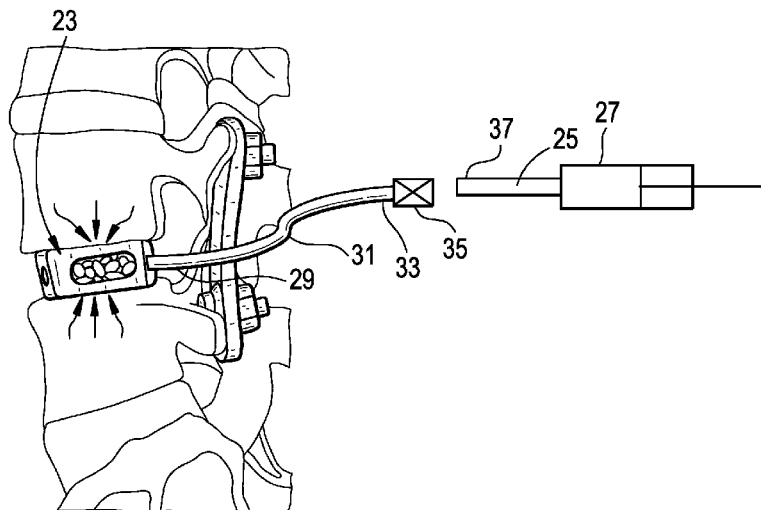
(52) **U.S. Cl.**

CPC **A61F 2/28** (2013.01); **A61F 2/2846** (2013.01); **A61F 2/441** (2013.01); **A61F 2/4465** (2013.01); **A61F 2/4611** (2013.01); **A61F 2/30965** (2013.01); **A61F 2/447** (2013.01); **A61F 2/4644** (2013.01); **A61F 2002/2817** (2013.01); **A61F 2002/2867** (2013.01); **A61F 2002/30062** (2013.01); **A61F 2002/3068** (2013.01); **A61F 2002/30588** (2013.01); **A61F 2002/30677** (2013.01); **A61F 2002/30841** (2013.01); **A61F 2002/4685** (2013.01); **A61F 2310/00017** (2013.01); **A61F**

(57) **ABSTRACT**

Devices and methods for in situ drawing, filtering and seeding cells from the marrow of surrounding bone into a fusion cage without any of the challenges mentioned above. Various implants and devices with aspiration ports that enable in-situ harvesting and mixing of stem cells. These devices may include spinal fusion cages, long bone spacers, lateral grafts and joint replacement devices. Each device utilizes at least one aspiration port for harvesting of stem cell-containing marrow via aspiration from adjacent bony elements.

22 Claims, 16 Drawing Sheets



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FIG. 1A

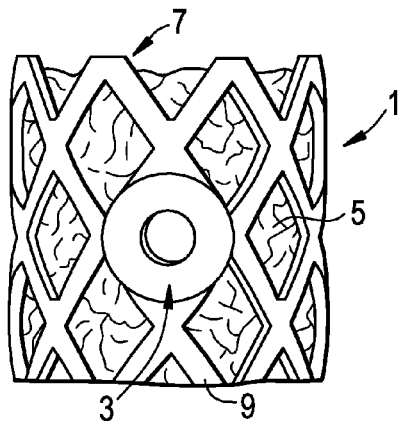


FIG. 1B

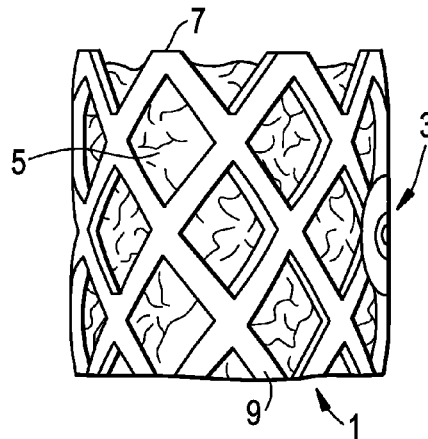


FIG. 1C

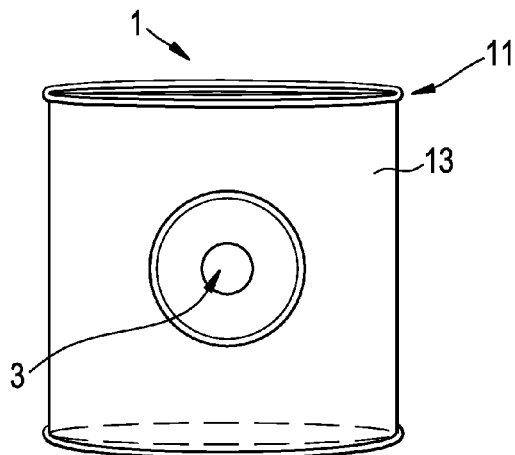


FIG. 1D

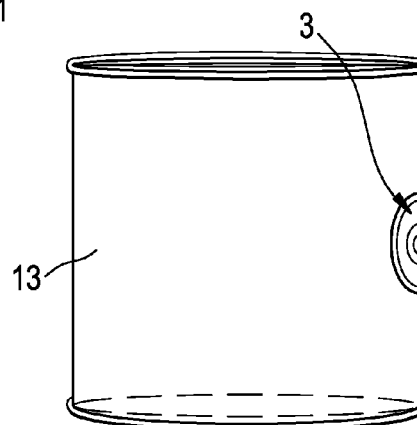


FIG. 2A

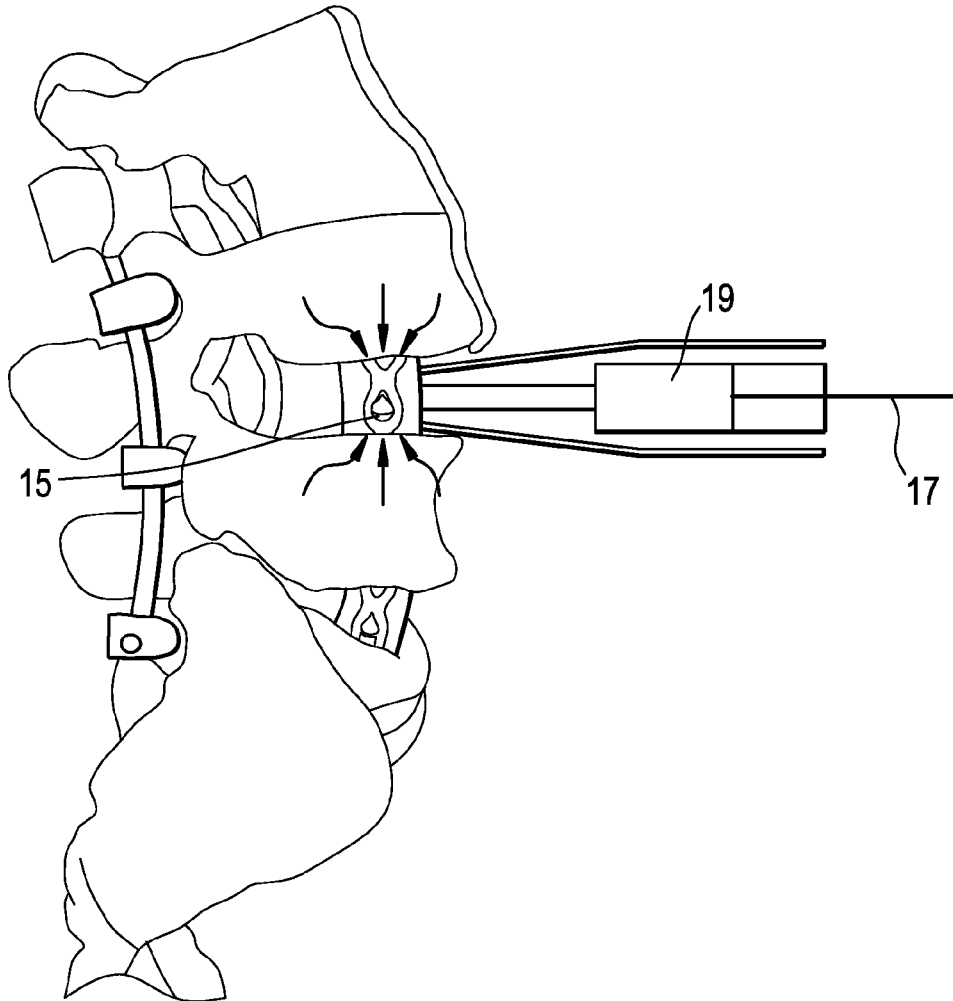


FIG. 2B

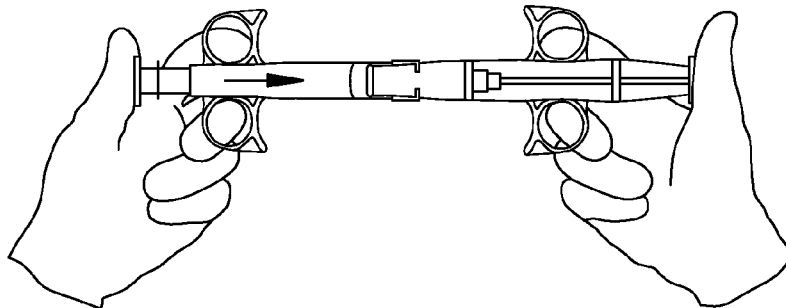


FIG. 3A

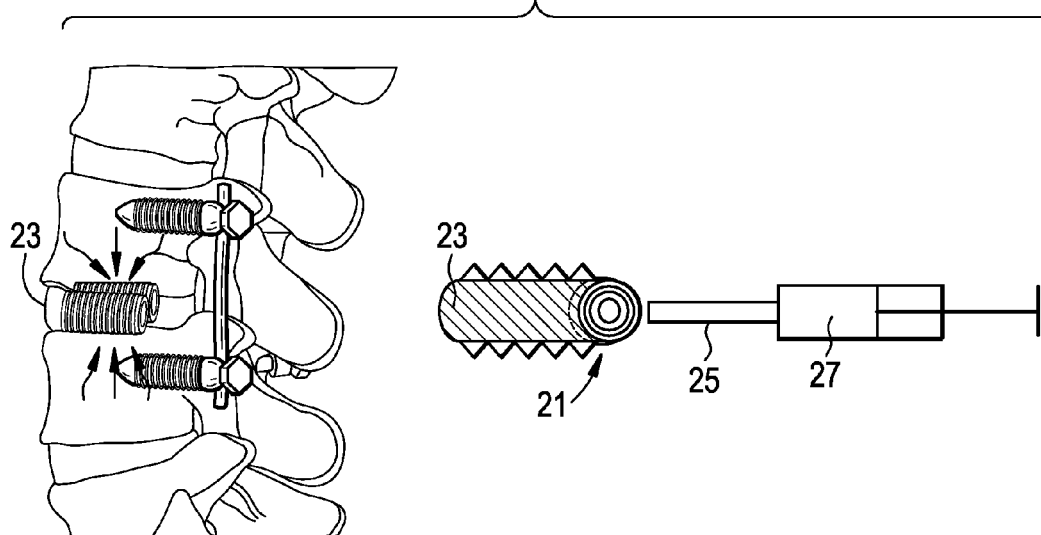


FIG. 3B

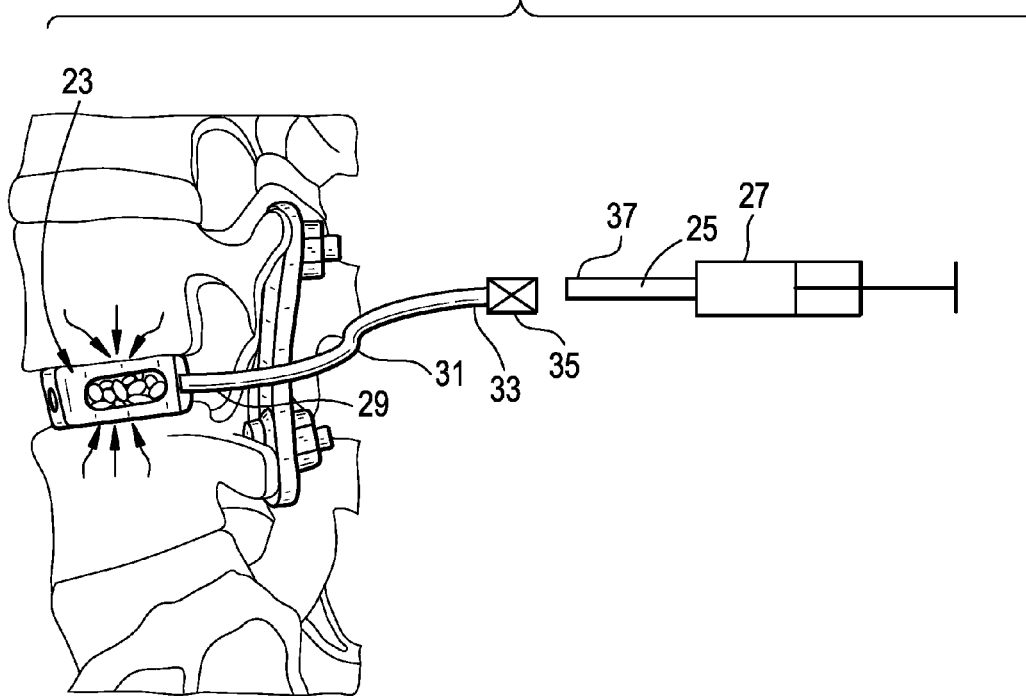


FIG. 3C

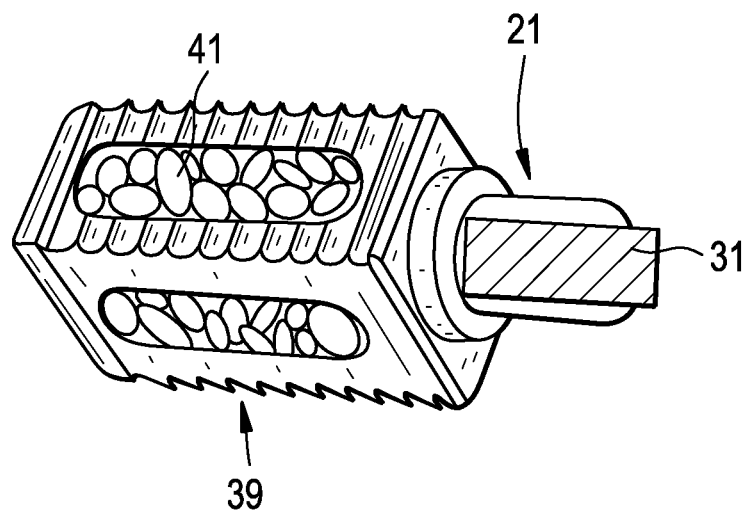


FIG. 3D

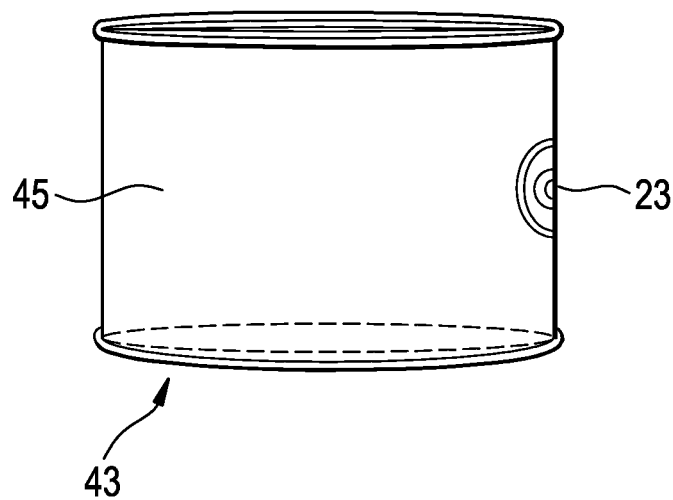


FIG. 4A

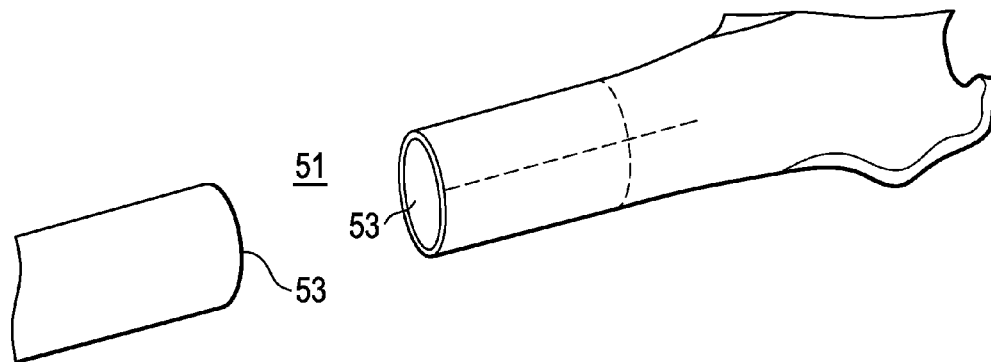


FIG. 4B

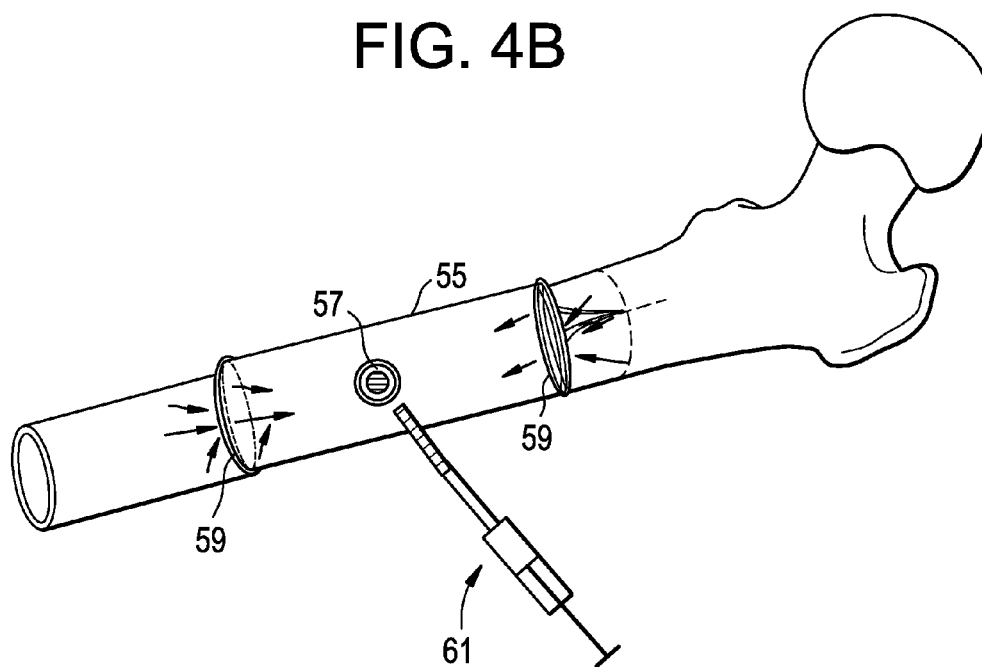


FIG. 5A

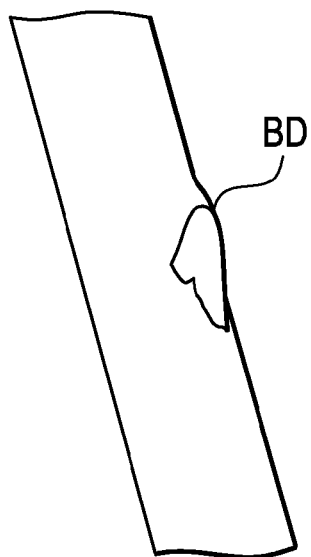


FIG. 5B

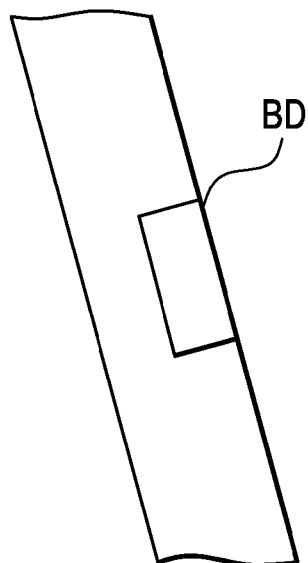


FIG. 5C

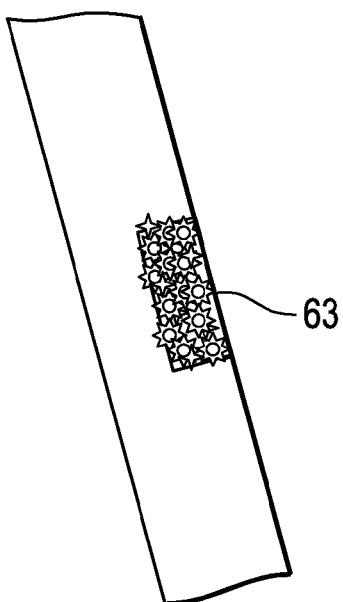


FIG. 5D

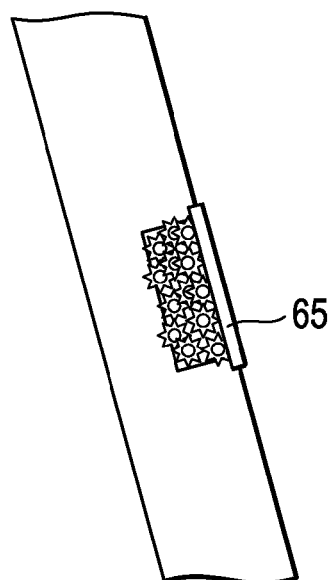


FIG. 5E

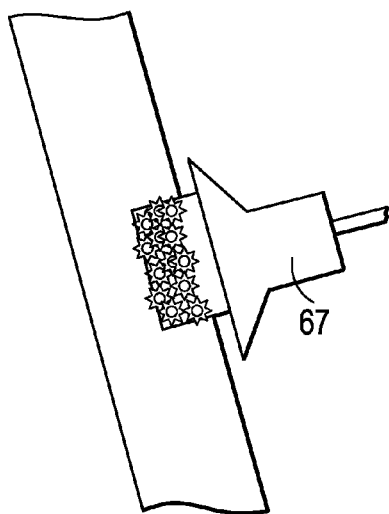


FIG. 5F

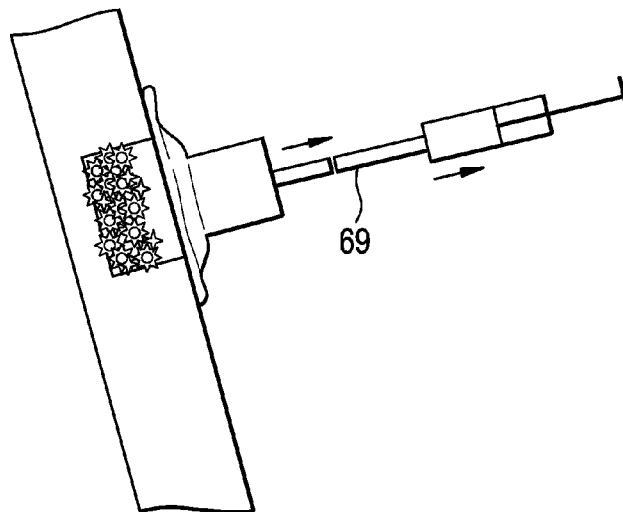


FIG. 6

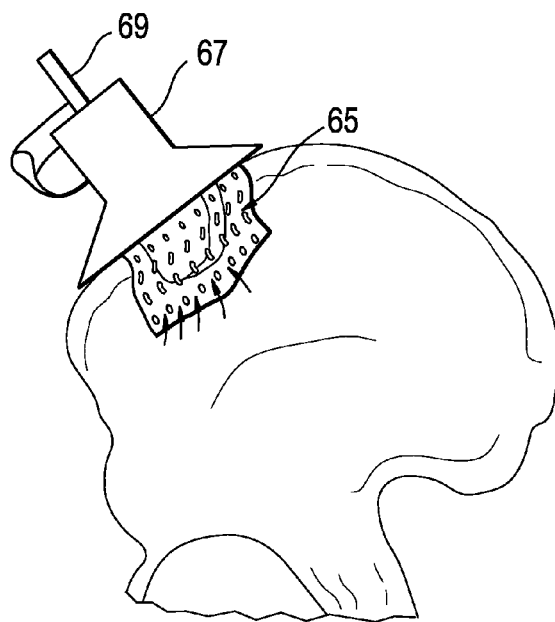


FIG. 7A

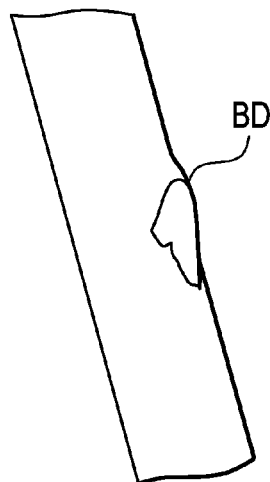


FIG. 7B

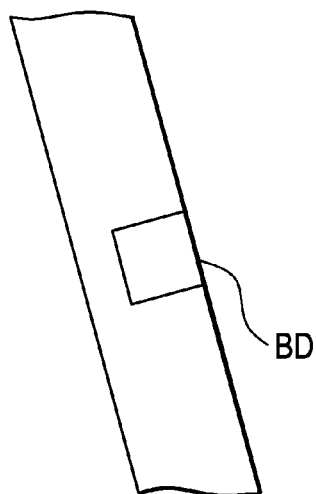


FIG. 7C

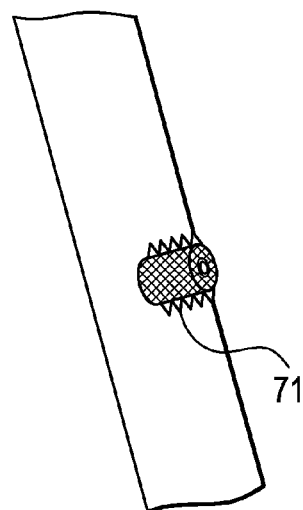


FIG. 7D

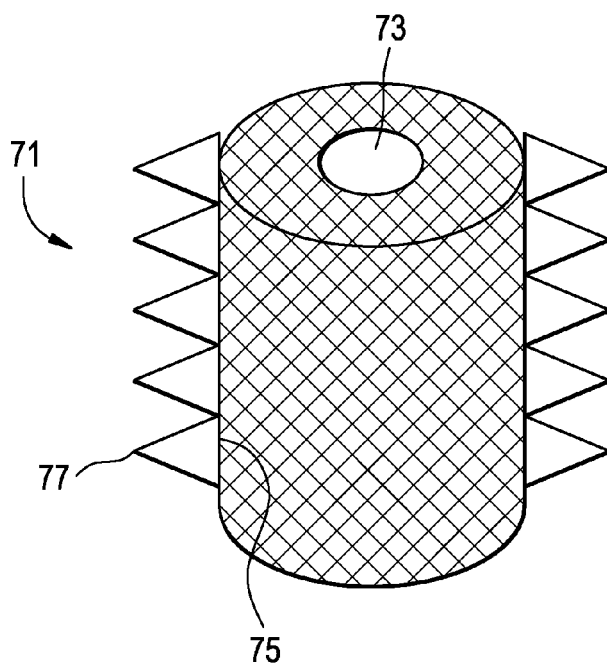


FIG. 7E

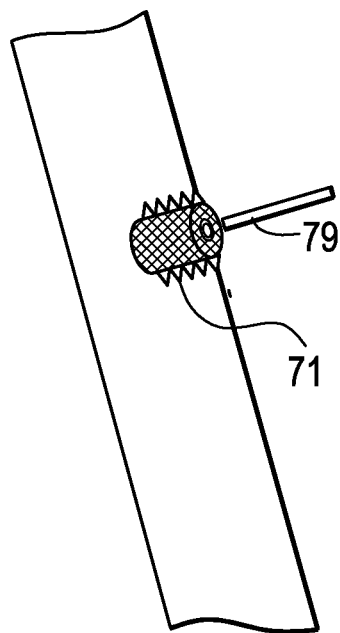


FIG. 7F

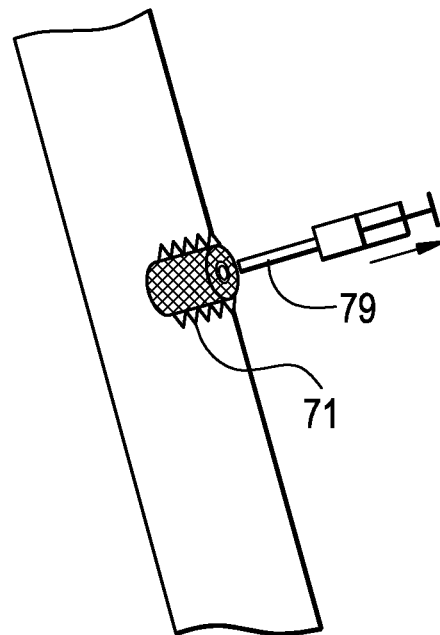


FIG. 8

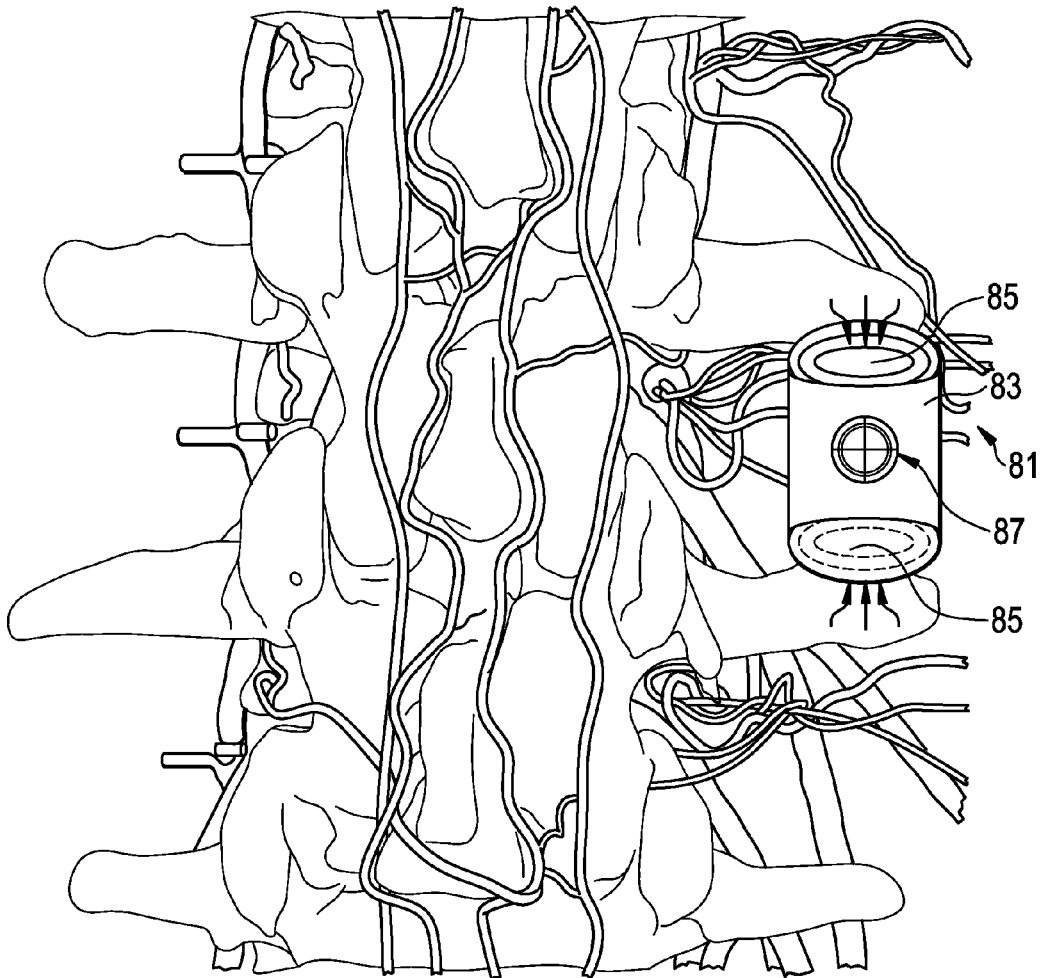


FIG. 9

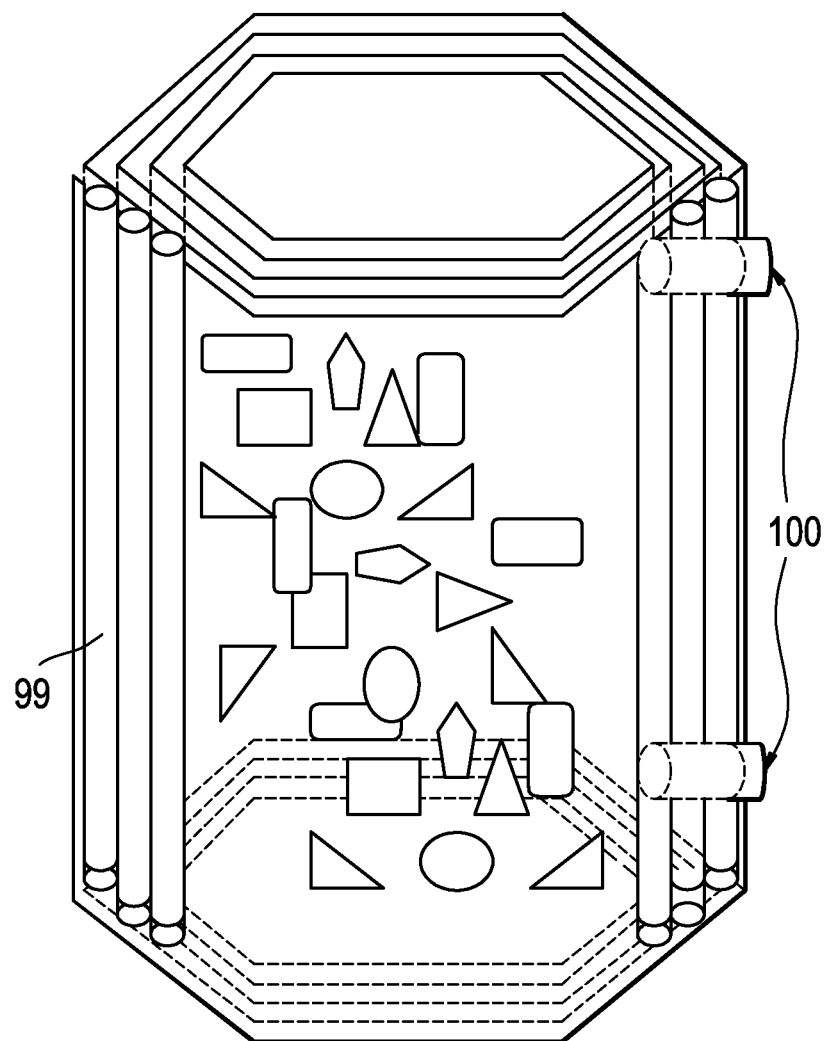


FIG. 10A

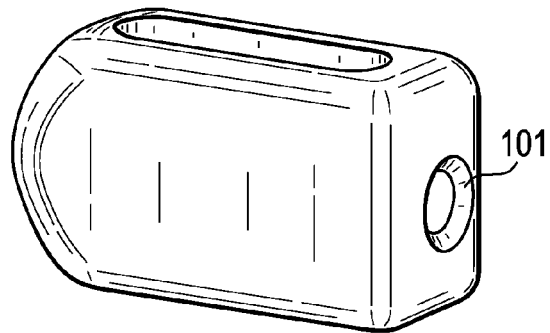


FIG. 10B

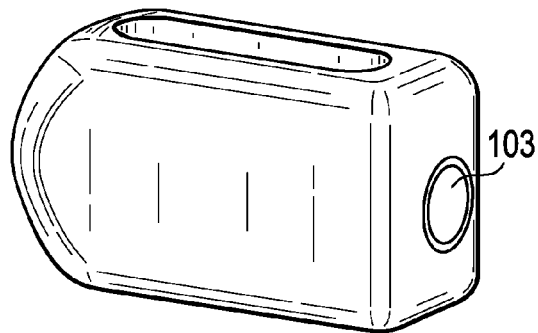


FIG. 10C

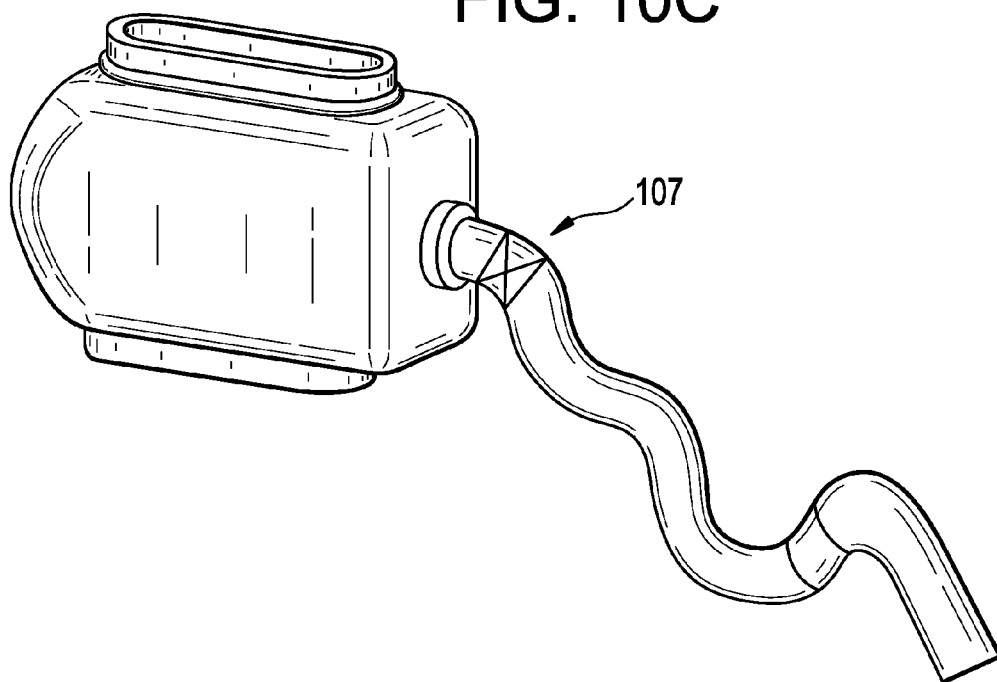


FIG. 10D

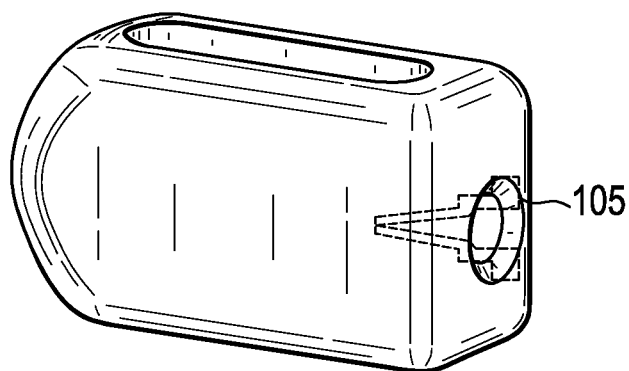


FIG. 10E

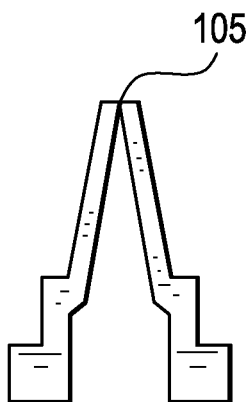


FIG. 10F

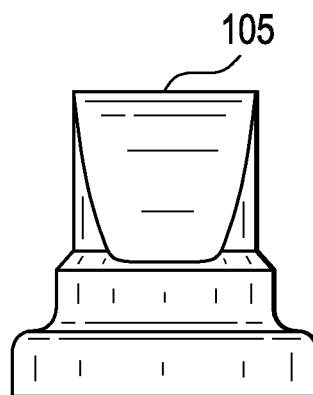


FIG. 11

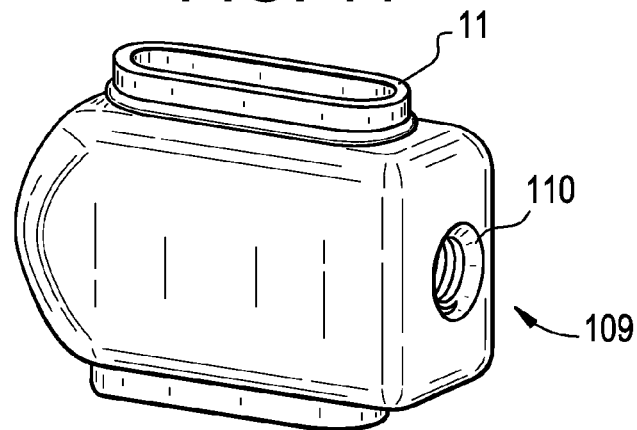


FIG. 12

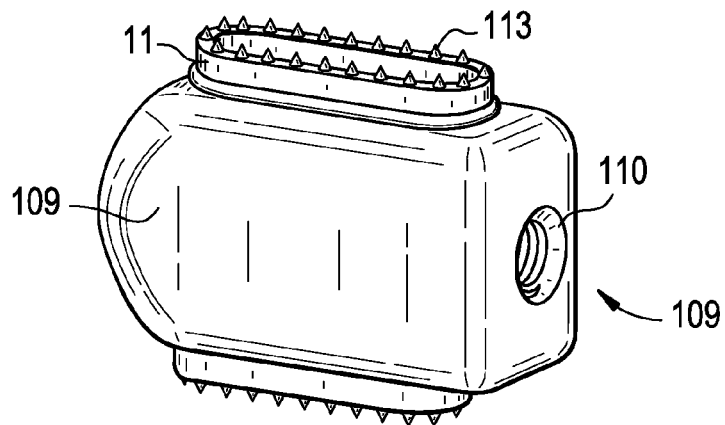


FIG. 13

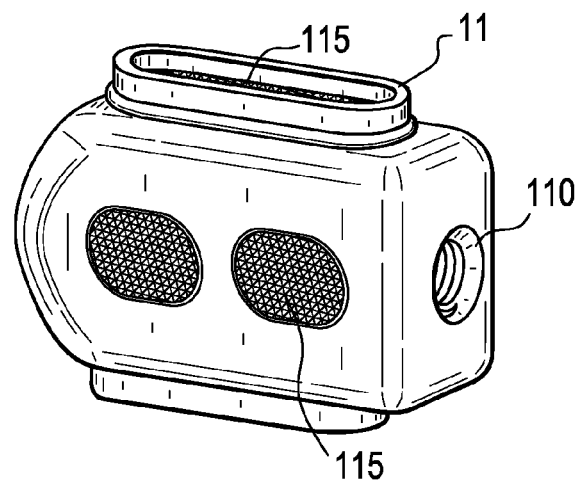


FIG. 14A

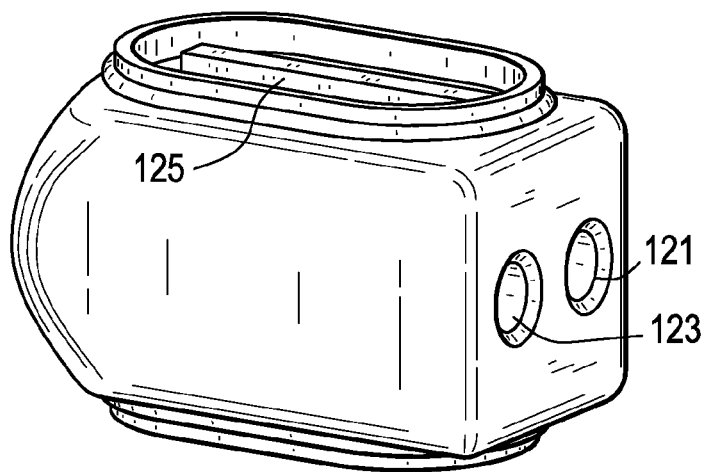


FIG. 14B

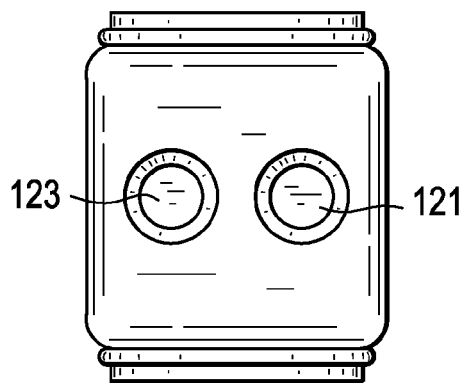


FIG. 14C

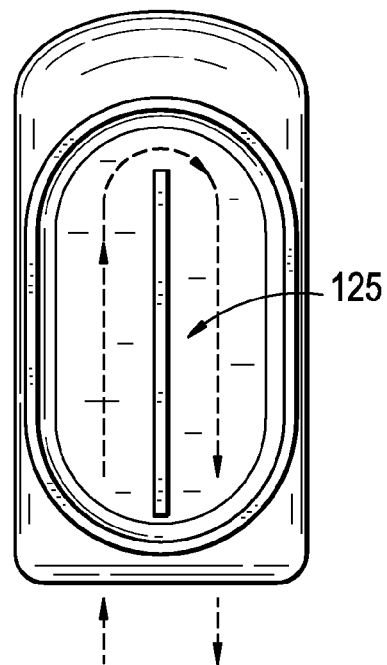
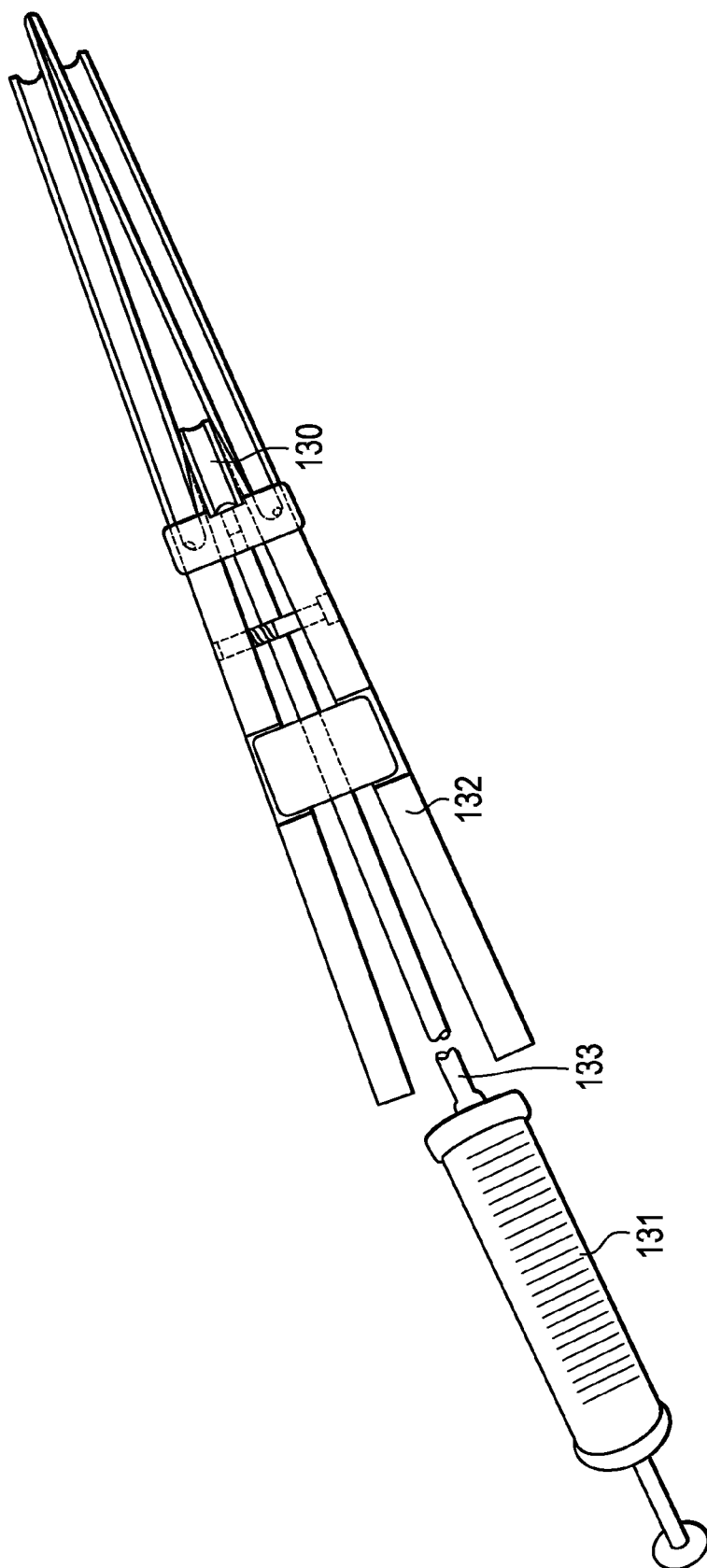


FIG. 15



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ASPIRATING IMPLANTS AND METHOD OF BONY REGENERATION

BACKGROUND OF THE INVENTION

Because bone regeneration is generally required to obtain successful outcomes for many common orthopedic procedures, osteoregenerative products such as allograft, bone substitutes, morphogenic proteins and osteoregenerative mixes are widely used by clinicians. In these procedures, both compression-resistant and non-compression resistant bone substitutes are frequently mixed with allograft as well as autologous materials including marrow and bone.

Current procedures for harvesting autologous stem cells from bone marrow have incorporated methods to enhance stem cell filtering, mixing or seeding to improve viability of implant matrixes. For example, U.S. Pat. No. 5,824,084 (Muschler) discloses a method of preparing a composite bone graft. Unfortunately, some disadvantages are associated with these procedures. For example, the time and exposure required during the mixing of bone, bone substitutes matrix's with autologous bone or aspirate can significantly delay the surgical procedures, increasing the risk of infection and blood loss.

Also, the bone marrow aspiration procedure often requires an added surgery for harvesting of BMA or bone from adjacent vertebrae, processes, ribs or the iliac crest. Spinal surgical fusion procedures require the endplates to be burred and roughened to allow marrow to bleed into the interbody graft. This added time and effort increases operating room demand, anesthesia requirements, infectious disease exposure, and blood loss, all of which impact patient outcomes as well as procedure cost. Lastly, conventional prefilled graft materials are not designed to maximize stem cell retention.

Thus, there is a need for a procedure and devices for harvesting stem cells that reduces collateral damage, infection risk, operating room time, operating room effort for graft mixing and packing, and provides a graft that enhances stem cell attachment.

US Published Patent Application No. 2008154377 (Voellmicke) discloses an intervertebral fusion cage that is adapted to contain an inserter within its inner volume during insertion of the cage.

Curylo, *Spine*, 24(5), 1 Mar. 1999, pp 434-438 discloses augmentation of spinal arthrodesis with autologous bone marrow in a rabbit posterolateral spine fusion model.

Božidar Šebečić, *Croatian Medical Journal*, March 1999 (Volume 40, Number 3) discloses percutaneous autologous bone marrow grafting on the site of tibial delayed union.

Becker, *Spine*, 31 (1), 2006, pp. 11-17, discloses osteopromotion by a β -tricalcium phosphate/bone marrow hybrid implant for use in spine surgery.

SUMMARY OF THE INVENTION

This invention provides devices and methods for the in-situ drawing, filtering and seeding of cells from the marrow of surrounding bone into an implanted fusion cage.

In particular, the present invention includes various implants with aspiration ports and other devices that enable in-situ harvesting and mixing of stem cells. These devices may include spinal fusion cages, long bone spacers, lateral grafts and joint replacement devices. Each implant utilizes at least one aspiration port for the in situ harvesting of stem cell-containing marrow via aspiration from adjacent decorticated bony elements.

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In some embodiments, some of the following components that enable stem cell collection are employed:

- fusion device aspiration ports,
- fusion device covers or sheaths that improve the suction through the cage;
- porous sheets that allow suction therethrough but retain cells,
- graft matrixes designed for controlled stem cell filtering, collection and bony regeneration, and
- insertion and aspiration instruments including a flexible aspiration funnel.

These components allow for effective retention of stem cells but without the time-consuming and invasive ex vivo harvesting, ex vivo mixing and ex vivo handling of conventionally-obtained graft.

Therefore, in accordance with the present invention, there is provided an intervertebral fusion assembly, comprising:

- a) an intervertebral fusion cage, comprising:
 - i) an upper surface adapted for gripping an upper vertebral body and comprising an upper throughhole therethrough,
 - ii) a lower surface adapted for gripping a lower vertebral body and comprising a lower throughhole therethrough,
 - iii) a sidewall connecting the upper and lower surfaces and comprising an aspiration port therethrough, and
- b) an aspirator,

wherein the aspirator connects to the aspiration port to provide fluid connection between the fusion cage and the aspirator.

DESCRIPTION OF THE FIGURES

FIGS. 1a-d discloses side and front views of intervertebral fusion cages of the present invention.

FIG. 2a discloses a side view of an assembly of the present invention, with the cage thereof implanted in a disc space.

FIG. 2b discloses use of the assembly.

FIG. 3a discloses an exploded assembly of the present invention.

FIG. 3b discloses a side view of another exploded assembly of the present invention, with the cage thereof implanted in a disc space.

FIG. 3c discloses a perspective view of an aspiration cage of the present invention.

FIG. 3d discloses a side view of an aspiration cage of the present invention wrapped in a graft containment bag (or sheath).

FIG. 4 discloses a tube-like load bearing device of the present invention implanted in a long bone.

FIGS. 5a-f disclose a method of the present invention being carried out in a long bone defect.

FIG. 6 discloses a method of the present invention being carried out on an iliac crest.

FIG. 7 discloses steps for implanting a long bone plug of the present invention in a contained bony defect.

FIG. 8 discloses an aspirating graft jacket implanted between adjacent transverse processes.

FIG. 9 discloses an aspirating graft jacket having nanotubes.

FIGS. 10a-d disclose cages of the present invention with various ports.

FIGS. 10e-f disclose side and front views of a duckbill-type enclosed valve.

FIG. 11 discloses an aspirating cage of the present invention having an endplate seal.

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FIG. 12 discloses an aspirating cage of the present invention in which the endplate seal has teeth extending therefrom.

FIG. 13 shows an aspirating cage of the present invention filled with a porous matrix.

FIGS. 14a-c show an aspirating cage of the present invention having two ports.

FIG. 15 discloses the cage of the present invention attached to an insertion device.

DETAILED DESCRIPTION OF THE INVENTION

Several aspirating devices and methods are disclosed that improve stem cell filtering, enhance mixing, increase bony regeneration, and reduce the risk of infection. These devices and methods include both implants and instruments that facilitate the in-situ aspiration and mixing of native autograft. The use of such devices and methods subsequently result in bone regeneration without the added operative procedure, manual variability and infection risk associated with the conventional harvesting and external mixing of stem cells.

In some embodiments, the aspiration port may be selected from the group consisting of a simple hole, a threaded hole, a pierceable membrane such as a septum, a cannulated projection extending out of the implant, and a recess extending into the implant. In some embodiments, the implant includes more than one such aspiration port.

The port (or aspiration line) may incorporate a one-way valve to enable aspiration while preventing subsequent leakage. The port (or aspiration line) may also have a bi-directional valve that enables both a) the aspiration of aspirate into the implant (by drawing a vacuum through the port), and b) the injection of biologics (such as cells, BMPs, drugs, anesthetics, analgesics, or antibiotics) directly into the porous matrix of the implant to enhance bone growth (by injecting through the port).

The ports may further include modular attachment means for intra-operative insertion, aspiration and/or injection.

The port may be designed to have a control feature that controls process variables such as flow rate, pressure and/or delivery of the aspirate through the porous bone substitute matrixes.

The implants may be in the form of a bag, tube or cage. They may be pre-operatively or intra-operatively filled with bone-inducing porous matrixes.

In the case of spinal fusion cages, openings in the bone-contacting surfaces (or endplates) of the cage enable marrow aspiration therethrough following aggravation of the natural endplates to initiate vascular/marrow flow. Such a cage having teeth on its endplates can be manipulated in-situ to decontaminate the bone and thereby enhance vascular flow and aspirate filtering. The spinal-fusion cage can have limited lateral/posterior holes to control vacuum pressure and maximize vascular flow. The endplates of the cage may include peripheral sealing as a means to enhance flow, fit, or conformation or provide for added vacuum capabilities with adjacent endplates. The cage can be fabricated with or placed within a bag (made of, for example, collagen or resorbable polymer) to contain vascularity and stem cells during and after aspiration.

Now referring to FIGS. 1a-d, there are provided front and side views of intervertebral fusion cages of the present invention. FIGS. 1a-b disclose a standard mesh-type cage 1 fitted with an aspiration port 3. The cage has been filled with a porous matrix 5 (in this case, a bony regeneration matrix) to assist in the retention of the stem cells in the cage. In some embodiments, the upper 7 and lower 9 surfaces of the cage have been beveled to increase endplate vascularity. FIGS. 1c-d disclose front and side views of the cages of FIGS. 1a-b,

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but with a sheath 13 wrapped around the cylindrical portion of the cage. These sheaths helped retain the suction produced by the aspiration.

Now referring to FIG. 2a, there is disclosed a side view of an assembly of the present invention, with the cage 15 thereof implanted in a disc space. In use, the plunger 17 of the aspiration syringe 19 is slowly withdrawn, thereby reducing the pressure in the air-tight cage. The low pressure in the cage causes bone marrow to move from the adjacent vertebral bodies into the cage (as shown by the plurality of arrows). The porous matrix provided in the cage retains the stem cells present in the marrow.

In some embodiments, the marrow collected in the syringe is re-injected through the cage in order to retain even more stem cells on the porous matrix.

FIG. 2b discloses use of the assembly.

Now referring to FIGS. 3a-d, there are provided various aspirator cages of the present invention. FIG. 3a discloses an exploded assembly of the present invention in which the port 21 of the cage 23 is aligned with the needle 25 of an aspirating syringe 27. In FIG. 3b, there is a side view of another exploded assembly of the present invention, with the cage 23 thereof implanted in a disc space. The distal end 29 of an aspiration line 31 is connected to the port 21 of the cage 23, while the proximal end 33 of the line is fitted with a valve 35. The purpose of the valve is to allow for disconnection without leakage. During aspiration, the valve will hold the negative pressure. During dispensing, the valve insures the dispensing pressure and prevents leakage. The valve can also control excess vacuum pressure for a predetermined time.

The valve is also adapted for connection to the distal end 37 of the needle of an aspirating syringe 27. FIG. 3c discloses a perspective view of an aspiration cage 39 of the present invention. This cage has a port 21 to which an aspiration line 31 is connected. The cage is also filled with porous matrix 41 for retaining the stem cells thereon. FIG. 3d discloses a side view of an aspiration cage 43 of the present invention wrapped in a graft containment bag 45 (or sheath).

The aspirating and filtering devices of the present invention can also be used to create long bone graft spacers with enhanced viability and reduced surgical risk. These tubular spacers may be fabricated from polymers, ceramics, or bone substitutes. They can be preoperatively or intra-operatively filled with porous bone substitute matrixes. Aspiration port(s) on the long bone spacer enable marrow aspiration and stem cell filtering to enhance viability of the device.

Therefore, and now referring to FIGS. 4a-b, there is provided a method of treating a long bone defect 51 having opposing cancellous surfaces 53, comprising the step of:

- inserting a fusion cage 55 into the defect, the cage having an aspiration port 57 and opposing porous endplates 59,
- orienting the cage so that each porous endplate of the cage abuts one of the cancellous surfaces,
- fluidly connecting an aspirator 61 to the port, and
- actuating the aspirator to lower pressure in the cage, thereby drawing bone marrow from the cancellous surfaces into the cage.

In one preferred embodiment, an implant of the present invention is used to improve the healing of a contained defect. In use, the defect is first filled with bone substitutes or matrixes and covered with an osteoconductive porous sheet or matrix. In-situ bone marrow (containing stem cells) is then aspirated through the porous sheet and the stem cells are seeded onto the matrix and sheet. This procedure may be accomplished with or without an aspiration port via a flexible

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and conforming funnel aspirator. The funnel can be deployed minimally invasively to both deliver and implant the porous sheet onto the defect.

Now referring to FIG. 5a, the procedure begins with creating an approach to the bony defect BD. Now referring to FIG. 5b, the defect BD is debrided. Now referring to FIG. 5c, the debrided area is filled with a porous matrix 63 (for example, a bone substitute or an expandable gel). Now referring to FIG. 5d, a porous cover sheet 65 is applied over the porous matrix housed in the debrided area. The cover sheet is then attached with either fasteners or an adhesive (neither shown). Now referring to FIG. 5e, a flexible aspiration funnel 67 is then laid upon the porous cover sheet. Now referring to FIG. 5f, an aspirator 69 is fluidly connected to the funnel, and a vacuum is drawn through the cover sheet to aspirate marrow into the porous matrix. The vacuum pressure associated with the aspiration is monitored and cut off when a desired pressure is obtained, or when the cover sheet or matrix becomes occluded with marrow.

Therefore, in accordance with the present invention, there is provided a method of treating a contained bony defect, comprising the steps of:

- a) debriding the bony defect,
- b) filling the defect with a porous matrix,
- c) placing a porous sheet over the porous matrix,
- d) placing a flexible funnel on the porous sheet, the funnel being fluidly connected to an aspirator, and
- e) actuating the aspirator to draw bone marrow from the defect into the porous matrix and cover sheet.

Now referring to FIG. 6, this flexible aspiration method described in FIGS. 5a-5f can also be utilized for other bony defects, including the iliac crest. Now referring to FIG. 6, there is provided a method of the present invention being carried out on an iliac crest, wherein the flexible funnel 67 and aspirator 69 draw bone marrow out of the pelvic region and into the porous matrix contained within the iliac crest so that the stem cells in the marrow are retained on the porous matrix.

Now referring to FIGS. 7a-f, contained defects can be filled with aspirating bone plugs 71 that include ports or covers to facilitate marrow aspiration and stem cell filtering. FIG. 7a discloses such a preferred device of the present invention.

Now referring to FIG. 7a, the procedure begins with creating an approach to the bony defect BD. Now referring to FIG. 7b, the defect BD is debrided. Now referring to FIG. 7c, the debrided area is filled with a fusion device 71 consisting essentially of inorganic bone or bone substitute. FIG. 7d shows a side view of the fusion device of FIG. 7c. This allograft device is cylindrical in structure and made from a portion of a human femoral, tibial or ulnar long bone. On one end of the device, there is an aspiration port 73 adapted for connection to an aspirator. On the peripheral surface 75 of the device, there are a plurality of securement features 77 (such as teeth). In some embodiments, the device is fabricated from bone substitute and made so that its pores facilitate growth in the longitudinal/axial direction. Now referring to FIG. 7e, an aspirator (such as a syringe 79) is fluidly connected to the port of the fusion device. Lastly, and now referring to FIG. 7f, aspiration is applied to draw marrow out of the adjacent bone and into the porous bone plug, wherein the stem cells are retained.

Therefore, in accordance with the present invention, there is provided a method of treating a contained bony defect, comprising the steps of:

- a) debriding the bony defect,
- b) filling the defect with a porous allograft plug,
- c) fluidly connecting the plug to an aspirator, and

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d) actuating the aspirator to draw bone marrow from the defect into the porous allograft plug.

In some embodiments, the bone substitutes can be in the form of prefabricated semi-porous bags that are placed within bony structures to enable aspiration of stem cell from adjacent bony structures. The "graft jacket" may be utilized for lateral graft in spinal procedures. This device is placed in a generally axial direction to provide intimate contact against opposing transverse processes, which can be intraoperatively burred to enhance vascularity.

Now referring to FIG. 8, there is provided an aspirating graft jacket of the present invention. The graft jacket 81 comprising:

- a) an expandable bag 83 having upper and lower through-holes 85 and an aspiration port 87, and
- b) a porous matrix (not shown) contained within the bag.

In use, the surgeon first aggravates the opposing faces of adjacent transverse processes in order to induce blood flow. Next, the surgeon places the aspirating graft jacket between the transverse processes, with the throughholes contacting the aggravated faces of the transverse processes. Next, the surgeon places an aspirator in fluid connection with the aspiration port of the graft jacket. Lastly, the surgeon applies a vacuum to the aspirator to draw marrow from the transverse processes and into the graft jacket.

Therefore, in accordance with the present invention, there is provided a method of fusing a spine between adjacent transverse processes, comprising the steps of:

- a) decorticating opposing faces of the adjacent transverse processes,
- b) placing a graft jacket having an aspiration port between the opposing faces so that upper and lower throughholes of the graft jacket contact the opposing faces,
- c) fluidly connecting the port to an aspirator, and
- d) actuating the aspirator to draw bone marrow from the transverse processes into the cage.

Now referring to FIG. 9, in some embodiments, the graft jacket of the present invention may contain nanotubes 99 extending longitudinally between the opposing open end-faces of the cage having ports 100. The axial nature of the nanotubes augments the load-bearing abilities of the graft jacket and further aids the capillary wicking of vascular flow to further enhance directional bone formation. Nanotubes can be produced from either carbon, metallics (titanium), polymers (such as PEEK, CFRP, or PET), or ceramics. Nanotubes can be produced from bone substitutes including CaP, HA, or TCP.

Now referring to FIGS. 10a-f, there are provided other embodiments of an intervertebral cage having a port. The port may be in the form of an opening 101 (as in FIG. 10a), a septum 103 (as in FIG. 10b), an enclosed valve 105 (as in FIG. 10d), or an in-line valve 107 (as in FIG. 10c). When an enclosed valve is selected, it is preferably in the form of a duckbill-type valve, as shown in FIGS. 10e and 10f. The port may be advantageously used for a) in-situ aspiration of autologous material (such as adjacent blood, marrow and stem cells); b) dispensing of bioactive materials (such as graft, INJECTOS, bone marrow aspirate, and growth factors such as BMPs); and c) re-dispensing of materials post operatively (such as in the event of a failed fusion).

Now referring to FIG. 11, there is provided another embodiment of the present invention describing a cage 109 with a port 110 and a compressible endplate seal 11. The compressible endplate seal typically lines an opening in the top or bottom of the cage and is made of elastomers (such as urethane, TPE, thermoplastic polymers and silicones), hydrogels, flexible resorbable polymers, or collagen. The com-

pressible endplate seal provides a number of advantageous functions, including enhancing endplate contact, enhancing vacuum of adjacent marrow, containing aspirate, and containing dispensate.

Therefore, in accordance with the present invention, there is provided an intervertebral fusion cage, comprising:

- a) an upper surface adapted for gripping an upper vertebral body and comprising an upper throughhole therethrough,
- b) a lower surface adapted for gripping a lower vertebral body and comprising a lower throughhole therethrough,
- c) a sidewall connecting the upper and lower surfaces and comprising an aspiration port therethrough, and

at least one compressible endplate seal disposed about either the upper or lower throughhole.

Now referring to FIG. 12, there is provided another embodiment of the present invention, describing a cage with a port, an endplate seal and a plurality of teeth 113 extending from the seal. The teeth may be used for gripping the opposing endplates and to initiate bleeding bone and marrow flow.

In some embodiments, the teeth that extend from the cage of the present invention are cannulated. These cannulated teeth can be deployed into the endplates once the cage is placed into the interbody space. In some embodiments, the inserter has a feature that triggers the spikes to deploy after insertion. Thus once the syringe is attached it would draw in marrow from the endplates through the holes in these cannulated teeth.

Now referring to FIG. 13, there is provided another embodiment of the present invention describing a cage with a port, an endplate seal with teeth, and a prefilled graft 115 within the cage. The graft acts as a filter to desirably increase stem cell selection/retention. In some embodiments, the graft has a pore size of between about 10 and about 20 μm and is treated with one or more of the following.

- a. Type 1 or 2 collagen,
- b. fibrinogen, fibronectin, and/or thrombin, or
- c. gelatin.

In some embodiments, a sheath (not shown) may be disposed around the cage of FIG. 13. The sheath may be used to advantageously enhance vacuum of adjacent marrow, contain aspirate, and contain dispensate.

Now referring to FIG. 14, there is provided another embodiment of the present invention describing a cage having two ports 121, 123. The pair of ports can be used to provide for dual aspiration. One of the ports can be a dedicated dispensing port for dispensing materials such as bone marrow aspirate, PRP, growth factors such as BMP. The dual ports can be used with a baffle 125 to set up circulation in the cage (with one port allowing inflow and the other allowing only outflow, as in FIG. 14 c). In one such circulation embodiment, the circulation provides for enhanced filtering. In another embodiment, recirculation is provided.

Now referring to FIG. 15, in some embodiments, the cage 130 may be inserted into the disc space with an inserter 132 substantially similar to that disclosed in U.S. Pat. Nos. 6,478,800 and 6,755,841 (the specifications of which are hereby incorporated by reference in their entirety), but with a syringe 131 and needle 133 replacing the medial shaft that connects with the implant.

In some embodiments, sufficient bone marrow is drawn into the cage to substantially fill the cage with bone marrow. However, it is known that stem cells selectively adhere to the surfaces of many porous media. Therefore, in other embodiments, an excess of bone marrow is drawn from the vertebral bodies and through the cage in order to concentrate the stem cells in the porous media of the cage.

The porous media is made from a biocompatible, implantable graft material. Preferably, the material has a charged surface. Examples of biocompatible, implantable graft materials having a charged surface include synthetic ceramics comprising calcium phosphate, some polymers, demineralized bone matrix, or mineralized bone matrix.

More preferably, cell adhesion molecules are bound to the surface of the porous media. The term "cell adhesion molecules" includes but is not limited to laminins, fibronectin, vitronectin, vascular cell adhesion molecules (V-CAM), intercellular adhesion molecules (I-CAM) and collagen.

In some embodiments, the cell adhesion molecule preferentially binds stem cells. In other embodiments, the cell adhesion molecule has a low affinity for partially or fully differentiated blood cells.

In some embodiments, the cage of the present invention includes a drug delivery reservoir. These reservoirs serve the same function as drug delivery microspheres but provide a more structured approach.

It is believed that a consistent and controlled flow rate of marrow through the cage will create the environment best suited for cell attachment. Preferably, the cage is designed (and the flow rate is selected) so that the flow of marrow therethrough fills the porous matrix in a reasonable time period, but does not flow so fast that shear stresses cause the stem cells to lyse.

The load-bearing fusion device of the present invention may be constructed of metals (such as Ti, Ti64, CoCr, and stainless steel), polymers (such as PEEK, polyethylene, polypropylene, and PET), resorbable polymers (such as PLA, PDA, PEO, PEG, PVA, and caprolactides), and allograft, bone substitutes (such as TCP, HA, and CaP).

The fusion device housing of the present invention can be made of any structural biocompatible material including resorbable (PLA, PLGA, etc.), non-resorbable polymers (CFRP, PEEK, UHMWPE, PDS), metallics (SS, Ti-6Al-4V, CoCr, etc.), as well as materials that are designed to encourage bony regeneration (allograft, bone substitute-loaded polymers, growth factor-loaded polymers, ceramics, etc.). The materials for the fusion device housing are biocompatible and generally similar to those disclosed in the prior art. Examples of such materials are metal, PEEK and ceramic.

In preferred embodiments, the fusion device housing is manufactured from a material that possesses the desirable strength and stiffness characteristics for use as a fusion cage component. These components of the present invention may be made from any non-resorbable material appropriate for human surgical implantation, including but not limited to, surgically appropriate metals, and non-metallic materials, such as carbon fiber composites, polymers and ceramics.

In some embodiments, the cage material is selected from the group consisting of PEEK, ceramic and metallic. The cage material is preferably selected from the group consisting of metal and composite (such as PEEK/carbon fiber).

If a metal is chosen as the material of construction for a component, then the metal is preferably selected from the group consisting of titanium, titanium alloys (such as Ti-6Al-4V), chrome alloys (such as CrCo or Cr—Co—Mo) and stainless steel.

If a polymer is chosen as a material of construction for a component, then the polymer is preferably selected from the group consisting of polyesters, (particularly aromatic esters such as polyalkylene terephthalates, polyamides; polyalkenes; poly(vinyl fluoride); PTFE; polyarylethyl ketone PAEK; polyphenylene and mixtures thereof.

If a ceramic is chosen as the material of construction for a component, then the ceramic is preferably selected from the

group consisting of alumina, zirconia and mixtures thereof. It is preferred to select an alumina-zirconia ceramic, such as BIOLOX Delta™, available from CeramTec of Plochingen, Germany.

In some embodiments, the cage member comprises PEEK. In others, it is a ceramic.

In some embodiments, the fusion device housing consists essentially of a metallic material, preferably a titanium alloy or a chrome-cobalt alloy.

In some embodiments, the fusion device housing components are made of a stainless steel alloy, preferably BioDur® CCM Plus® Alloy available from Carpenter Specialty Alloys, Carpenter Technology Corporation of Wyomissing, Pa. In some embodiments, the fusion device housing components are coated with a sintered beadcoating, preferably Poro-coat™, available from DePuy Orthopaedics of Warsaw, Ind.

In some embodiments, the fusion device housing is made from a composite comprising carbon fiber. Composites comprising carbon fiber are advantageous in that they typically have a strength and stiffness that is superior to neat polymer materials such as a polyarylethyl ketone PAEK. In some embodiments, the fusion device housing is made from a polymer composite such as a PEKK-carbon fiber composite.

Preferably, the composite comprising carbon fiber further comprises a polymer. Preferably, the polymer is a polyarylethyl ketone (PAEK). More preferably, the PAEK is selected from the group consisting of polyetherether ketone (PEEK), polyether ketone ketone (PEKK) and polyether ketone (PEK). In preferred embodiments, the PAEK is PEEK.

In some embodiments, the carbon fiber comprises between 1 vol % and 60 vol % (more preferably, between 10 vol % and 50 vol %) of the composite. In some embodiments, the polymer and carbon fibers are homogeneously mixed. In others, the material is a laminate. In some embodiments, the carbon fiber is present in a chopped state. Preferably, the chopped carbon fibers have a median length of between 1 mm and 12 mm, more preferably between 4.5 mm and 7.5 mm. In some embodiments, the carbon fiber is present as continuous strands.

In especially preferred embodiments, the composite comprises:

- a) 40-99% (more preferably, 60-80 vol %) polyarylethyl ketone (PAEK), and
 - b) 1-60% (more preferably, 20-40 vol %) carbon fiber,
- wherein the polyarylethyl ketone (PAEK) is selected from the group consisting of polyetherether ketone (PEEK), polyether ketone ketone (PEKK) and polyether ketone (PEK).

In some embodiments, the composite consists essentially of PAEK and carbon fiber. More preferably, the composite comprises 60-80 wt % PAEK and 20-40 wt % carbon fiber. Still more preferably the composite comprises 65-75 wt % PAEK and 25-35 wt % carbon fiber.

In general, the housing is typically filled with at least one bone forming agent (BFA). The bone-forming agent may be:

- a) a growth factor (such as an osteoinductive or angiogenic factor),
- b) osteoconductive (such as a porous matrix of granules),
- c) osteogenic (such as viable osteoprogenitor cells), or
- d) plasmid DNA.

In some embodiments, the housing contains a liquid carrier, and the bone forming agent is soluble in the carrier.

In some embodiments, the bone forming agent is a growth factor. As used herein, the term "growth factor" encompasses any cellular product that modulates the growth or differentiation of other cells, particularly connective tissue progenitor cells. The growth factors that may be used in accordance with the present invention include, but are not limited to, members

of the fibroblast growth factor family, including acidic and basic fibroblast growth factor (FGF-1 and FGF-2) and FGF-4; members of the platelet-derived growth factor (PDGF) family, including PDGF-AB, PDGF-BB and PDGF-AA; EGFs; VEGF; members of the insulin-like growth factor (IGF) family, including IGF-I and -II; the TGF- β superfamily, including TGF- β 1, 2 and 3; osteoid-inducing factor (OIF), angiogenin (s); endothelins; hepatocyte growth factor and keratinocyte growth factor; members of the bone morphogenetic proteins (BMPs) BMP-1, BMP-3, BMP-2, OP-1, BMP-2A, BMP-2B, BMP-7 and BMP-14, including HBGF-1 and HBGF-2; growth differentiation factors (GDFs), members of the hedgehog family of proteins, including indian, sonic and desert hedgehog; ADMP-1; bone-forming members of the interleukin (IL) family; rhGDF-5; and members of the colony-stimulating factor (CSF) family, including CSF-1, G-CSF, and GM-CSF; and isoforms thereof.

In some embodiments, platelet concentrate is provided as the bone forming agent. In one embodiment, the growth factors released by the platelets are present in an amount at least two-fold (e.g., four-fold) greater than the amount found in the blood from which the platelets were taken. In some embodiments, the platelet concentrate is autologous. In some embodiments, the platelet concentrate is platelet rich plasma (PRP). PRP is advantageous because it contains growth factors that can restimulate the growth of the bone, and because its fibrin matrix provides a suitable scaffold for new tissue growth.

In some embodiments, the bone forming agent comprises an effective amount of a bone morphogenetic protein (BMP). BMPs beneficially increase bone formation by promoting the differentiation of mesenchymal stem cells (MSCs) into osteoblasts and their proliferation.

In some embodiments, between about 1 ng and about 10 mg of BMP are administered into the target disc space. In some embodiments, between about 1 microgram (μ g) and about 1 mg of BMP are administered into the target disc space.

In many preferred embodiments, the bone forming agent is a porous matrix, and is preferably injectable.

The porous matrix of the present invention may contain porous or semi-porous collagen, extracellular matrices, metals (such as Ti, Ti64, CoCr, and stainless steel), polymers (such as PEEK, polyethylene, polypropylene, and PET) resorbable polymers (such as PLA, PDA, PEO, PEG, PVA, and caprolactides), bone substitutes (such as TCP, HA, and CaP), autograft, allograft, xenograft, and/or blends thereof. Matrices may be orientated to enable flow from bony attachment locations to the aspiration port. Matrices may be layered with varying densities, pore structures, materials to enable increase stem filter at desired locations via density, pore size, affinity, as well as fluid flow control (laminar, turbulent, and/or tortuous path).

In some embodiments, the porous matrix is a mineral. In one embodiment, this mineral comprises calcium and phosphorus. In some embodiments, the mineral is selected from the group consisting of calcium phosphate, tricalcium phosphate and hydroxyapatite. In one embodiment, the average porosity of the matrix is between about 20 and about 500 μ m, for example, between about 50 and about 250 μ m. In yet other embodiments of the present invention, in situ porosity is produced in the injected matrix to produce a porous scaffold in the interbody space. Once the in situ porosity is produced in the space, the surgeon can inject other therapeutic compounds into the porosity, thereby treating the surrounding tissues and enhancing the remodeling process of the target tissue.

In some embodiments, the mineral is administered in a granule form. It is believed that the administration of granular minerals promotes the formation of the bone growth around the minerals such that osteointegration occurs.

In some embodiments, the mineral is administered in a settable-paste form. In this condition, the paste sets up in vivo, and thereby immediately imparts post-treatment mechanical support to the interbody space.

In another embodiment, the treatment is delivered via injectable absorbable or non-absorbable cement to the target space. The treatment is formulated using bioabsorbable macro-sphere technologies, such that it will allow the release of the bone forming agent. The cement will provide the initial stability required to treat pain in target tissues. These tissues include, but are not limited to, hips, knee, vertebral body and iliac crest. In some embodiments, the cement is selected from the group consisting of calcium phosphate, tricalcium phosphate and hydroxyapatite. In other embodiments, the cement is any hard biocompatible cement, including PMMA, processed autogenous and allograft bone. Hydroxylapatite is a preferred cement because of its strength and biological profile. Tricalcium phosphate may also be used alone or in combination with hydroxylapatite, particularly if some degree of resorption is desired in the cement.

In some embodiments, the porous matrix comprises a resorbable polymeric material.

In some embodiments, the bone forming agent comprises an injectable precursor fluid that produces the in situ formation of a mineralized collagen composite. In some embodiments, the injectable precursor fluid comprises:

- a) a first formulation comprising an acid-soluble type I collagen solution (preferably between about 1 mg/ml and about 7 mg/ml collagen) and
- b) a second formulation comprising liposomes containing calcium and phosphate.

Combining the acid-soluble collagen solution with the calcium- and phosphate-loaded liposomes results in a liposome/collagen precursor fluid, which, when heated from room temperature to 37° C., forms a mineralized collagen gel.

In some embodiments, the liposomes are loaded with dipalmitoylphosphatidylcholine (90 mol %) and dimyristoyl phosphatidylcholine (10 mol %). These liposomes are stable at room temperature but form calcium phosphate mineral when heated above 35° C., a consequence of the release of entrapped salts at the lipid chain melting transition. One such technology is disclosed in Pederson, *Biomaterials* 24: 4881-4890 (2003), the specification of which is incorporated herein by reference in its entirety.

Alternatively, the in situ mineralization of collagen could be achieved by an increase in temperature achieved by other types of reactions including, but not limited to, chemical, enzymatic, magnetic, electric, photo- or nuclear. Suitable sources thereof include light, chemical reaction, enzymatically controlled reaction and an electric wire embedded in the material. To further elucidate the electric wire approach, a wire can first be embedded in the space, heated to create the calcium deposition, and then withdrawn. In some embodiments, this wire may be a shape memory such as nitinol that can form the shape. Alternatively, an electrically-conducting polymer can be selected as the temperature raising element. This polymer is heated to form the collagen, and is then subject to disintegration and resorption in situ, thereby providing space adjacent the mineralized collagen for the bone to form.

In some embodiments, the osteoconductive material comprises calcium and phosphorus. In some embodiments, the osteoconductive material comprises hydroxyapatite. In some

embodiments, the osteoconductive material comprises collagen. In some embodiments, the osteoconductive material is in a particulate form.

Specific matrices may be incorporated into the device to provide load bearing qualities, enable directional bone formation, and/or control density of regenerated bone (cortical vs cancellous) or enable cell formation for soft tissue attachment. Nanotubes or nanocrystals can be orientated in a generally axial direction to provide for load bearing abilities as well as capillary wicking of vascular flow to further enhance directional bone formation. Biocompatible nanotubes can currently be produced from either carbon or titanium or bone substitutes including Ca, HA, and TCP.

In one embodiment, the bone forming agent is a plurality of viable ex vivo osteoprogenitor cells. Such viable cells, introduced into the interbody space, have the capability of at least partially supplementing the in situ drawn stem cells in the generation of new bone for the interbody space.

In some embodiments, these cells are obtained from another human individual (allograft), while in other embodiments, the cells are obtained from the same individual (autograft). In some embodiments, the cells are taken from bone tissue, while in others, the cells are taken from a non-bone tissue (and may, for example, be mesenchymal stem cells, chondrocytes or fibroblasts). In others, autograft osteocytes (such as from the knee, hip, shoulder, finger or ear) may be used.

In one embodiment, when viable ex vivo cells are selected as an additional therapeutic agent or substance, the viable cells comprise mesenchymal stem cells (MSCs). MSCs provide a special advantage for administration into the interbody space because it is believed that they can more readily survive the relatively harsh environment present in the space; that they have a desirable level of plasticity; and that they have the ability to proliferate and differentiate into the desired cells.

In some embodiments, the mesenchymal stem cells are obtained from bone marrow, such as autologous bone marrow. In others, the mesenchymal stem cells are obtained from adipose tissue, preferably autologous adipose tissue.

In some embodiments, the mesenchymal stem cells injected into the interbody space are provided in an unconcentrated form, e.g., from fresh bone marrow. In others, they are provided in a concentrated form. When provided in concentrated form, they can be uncultured. Uncultured, concentrated MSCs can be readily obtained by centrifugation, filtration, or immuno-absorption. When filtration is selected, the methods disclosed in U.S. Pat. No. 6,049,026 ("Muschler"), the specification of which is incorporated herein by reference in its entirety, can be used. In some embodiments, the matrix used to filter and concentrate the MSCs is also administered into the interbody space.

In some embodiments, bone cells (which may be from either an allogeneic or an autologous source) or mesenchymal stem cells, may be genetically modified to produce an osteoinductive bone anabolic agent which could be chosen from the list of growth factors named herein. The production of these osteopromotive agents may lead to bone growth.

Recent work has shown that plasmid DNA will not elicit an inflammatory response as does the use of viral vectors. Genes encoding bone (anabolic) agents such as BMP may be efficacious if injected into the uncoupled resorbing bone. In addition, overexpression of any of the growth factors provided herein or other agents which would limit local osteoclast activity would have positive effects on bone growth. In one embodiment, the plasmid contains the genetic code for human TGF- β or erythropoietin (EPO).

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Accordingly, in some embodiments, the additional therapeutic agent is selected from the group consisting of viable cells and plasmid DNA.

A matrix may be made from hydrogels or may incorporate a hydrogel as component of the final structure. A hydrogel may be used to expand and enhance filling, improve handling characteristics or increase vacuum pressure. The increased vacuum pressure may be used to determine adequate hydration/stem cell filtration.

In all cases, excess bone marrow aspirate can be collected and mixed with added graft extenders including collagen like the HEALOS™, INJECTOS™ and HEALOS FX™, each of which is available from DePuy Spine Inc, Raynham, Mass., USA.

Although the present invention has been described with reference to its preferred embodiments, those skillful in the art will recognize changes that may be made in form and structure which do not depart from the spirit of the invention.

We claim:

1. An intervertebral fusion assembly, comprising:

a) an intervertebral fusion cage, comprising:

i) an upper surface adapted for gripping an upper vertebral body and comprising an upper throughhole therethrough,

ii) a lower surface adapted for gripping a lower vertebral body and comprising a lower throughhole therethrough,

iii) a sidewall connecting the upper and lower surfaces and comprising an aspiration port therethrough, and

b) an aspirator,

wherein the aspirator connects to the aspiration port to provide fluid connection between the fusion cage and the aspirator,

wherein the aspiration port comprises a one-way valve that enables aspiration while preventing subsequent leakage, wherein at least one of the upper surface and lower surface includes a compressible seal lining its throughhole.

2. The assembly of claim 1 wherein the aspiration port is selected from the group consisting of a hole, a pierceable membrane, a cannulated projection extending out of the cage, and a recess into the cage.

3. The assembly of claim 1 wherein the aspiration port has a lock fitting, and the aspirator has a mating lock fitting.

4. The assembly of claim 1 wherein the cage comprises more than one aspiration port.

5. The assembly of claim 1 wherein the port comprises a modular attachment means.

6. The assembly of claim 5 wherein the modular attachment means is selected from the group consisting of an insertion means, an aspiration means and an injection means.

7. The assembly of claim 1 wherein the port comprises a control feature that controls the flow rate, pressure or delivery of the aspirate through the cage.

8. The assembly of claim 1 wherein the cage further comprises a fluid-tight jacket wrapped around the sidewall.

9. The assembly of claim 1 wherein the aspirator is a syringe.

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10. The assembly of claim 1 wherein the sidewall of the cage has at least one throughhole.

11. The assembly of claim 1 wherein the cage comprises a lateral or posterior hole adapted to control vacuum pressure and maximize vascular flow.

12. The assembly of claim 1 wherein the upper surface of the cage comprises a plurality of teeth.

13. The assembly of claim 1 wherein the upper surface of the cage comprises a plurality of cannulated teeth.

14. The assembly of claim 1 wherein the seal is selected from the group consisting of an elastomer, a hydrogel, a flexible resorbable polymer, and collagen.

15. The assembly of claim 1 wherein the seal is an elastomer selected from the group consisting of urethane, TPE, a thermoplastic polymer and a silicone.

16. An intervertebral fusion cage, comprising:

a) an upper surface adapted for gripping an upper vertebral body and comprising an upper throughhole therethrough,

b) a lower surface adapted for gripping a lower vertebral body and comprising a lower throughhole therethrough,

c) a sidewall connecting the upper and lower surfaces and comprising an aspiration port therethrough, and

d) at least one compressible endplate seal disposed about either the upper or lower throughhole,

wherein the aspiration port comprises a one-way valve that enables aspiration while preventing subsequent leakage, wherein the seal lines the throughhole.

17. The cage of claim 16 wherein the seal comprises a plurality of teeth thereon.

18. An interbody fusion assembly, comprising:

a) an interbody fusion device, comprising:

i) a housing comprising upper and lower endplates having upper and lower throughholes therethrough,

ii) a porous matrix contained within the housing,

iii) an aspiration port therethrough, and

b) an aspirator,

wherein the aspirator connects to the aspiration port to provide fluid connection between the fusion device and the aspirator,

wherein the aspiration port comprises a one-way valve that enables aspiration while preventing subsequent leakage, wherein at least one of the upper surface and lower surface includes a compressible seal surrounding the upper or lower throughhole.

19. The assembly of claim 18 wherein the housing comprises an expandable bag.

20. The assembly of claim 18 wherein the housing comprises a tube.

21. The assembly of claim 18 wherein the porous matrix is selected from the group consisting of porous or semi-porous collagen, an extracellular matrix, a metal, a polymer, a bone substitute, autograft, allograft, xenograft, and blends thereof.

22. The assembly of claim 18 wherein the porous matrix comprises a plurality of nanofilaments.

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